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Prolonged Survival of Patients Receiving Trastuzumab beyond Disease Progression for HER2 Overexpressing Metastatic Breast Cancer (MBC)

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Key Words

Trastuzumab · Breast cancer, metastatic · HER2 overexpression · Chemotherapy

Summary

Background: The aim of this retrospective analysis was to evaluate the impact of trastuzumab-based regimens on the survival of patients with HER2-overexpressing metastatic breast cancer (MBC). The study specifically focussed on the influence of the continuation of trastuzumab-based treatment despite tumor progression on survival. **Patients and Methods:** Patients with HER2 overexpressing MBC were included in this retrospective analysis. HER2 overexpression was determined by the immunohistochemical staining score (DAKO Hercep Test™). Trastuzumab was applied at a loading dose of 4 mg/kg and a maintenance dose of 2 mg/kg. **Results:** Among 136 HER2 overexpressing patients (DAKO score 3+), 66 patients received first-line trastuzumab, 47 patients received trastuzumab as second-line therapy and 23 patients received trastuzumab beyond disease progression. There was no significant difference regarding the duration of trastuzumab-based treatment (first-line: 29.5 weeks vs. second-line: 25 weeks). Moreover, there was no difference in the response rate (first-line: 37.9% vs. second-line: 35.7%) or the median survival (p = 0.47 log rank). Patients who received ≥ 2 trastuzumab-based regimens for MBC survived significantly longer compared to those who had received only 1 regimen (≥ 2 regimens: 62.4 months vs. 1 regimen: 38.5 months; p = 0.01 log rank). **Conclusions:** Trastuzumab is highly effective in the treatment of HER2 overexpressing MBC. Compared to historical controls, overall survival appears to be markedly prolonged, particularly in patients who received sequential trastuzumab-based treatment beyond disease progression.

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Schlüsselwörter

Trastuzumab · Mammakarzinom, metastasiertes · HER2-Überexpression · Chemotherapie

Zusammenfassung

Hintergrund: Ziel dieser retrospektiven Analyse war es, den Einfluss einer Trastuzumab-basierten Therapie auf die Überlebenszeit beim HER2-überexprimierenden metastasierten Mammakarzinom (MBC) zu erfassen. Hierbei interessierte vor allem, inwieweit die Fortsetzung einer Trastuzumab-basierten Therapie trotz Tumorprogression Einfluss auf die Überlebenszeit nimmt. **Patientinnen und Methoden:** Patientinnen mit HER2 überexprimierendem MBC wurden in diese retrospektive Analyse eingeschlossen. Der Grad der HER2-Überexpression wurde mittels Immunhistochemie bestimmt (DAKO-Hercep Test™). Trastuzumab wurde in einer Startdosis von 4 mg/kg und anschließend mit einer Erhaltungsdosis von 2 mg/kg verabreicht. **Ergebnisse:** Von 136 HER2-überexprimierenden Patientinnen (DAKO score 3+) wurden 66 Patientinnen mit einer first-line und 47 Patientinnen mit einer second-line Trastuzumab-basierten Therapie behandelt. 23 Patientinnen erhielten eine Trastuzumab-basierte Therapie über die Tumorprogression hinaus. Es bestand kein signifikanter Unterschied bezüglich der Dauer einer Trastuzumab-basierten Therapie (first-line: 29,5 Wochen vs. second-line: 25 Wochen), der Ansprechraten (first-line: 37,9% vs. second-line: 35,7%) und der medianen Überlebenszeit (p = 0,47 log rank). Allerdings lebten Patientinnen, die bei Progression erneut mit einer Trastuzumab-basierten Therapie behandelt wurden, signifikant länger als diejenigen Patientinnen, bei denen Trastuzumab bei Progression abgesetzt wurde (≥ 2 Therapien: 62,4 vs. 1 Therapie: 38,5 Monate; p = 0,01 log rank). **Schlussfolgerungen:** Trastuzumab ist hoch effektiv in der Behandlung des HER2-überexprimierenden Mammakarzinoms. Im Vergleich zu historischen Kontrollen ist die Überlebenszeit deutlich verlängert, vor allem bei Patientinnen, die bei Progression mit einer erneuten Trastuzumab-basierten Therapie behandelt werden.

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Introduction

Trastuzumab (Herceptin™, Genentech, San Francisco, CA, USA) is a humanized monoclonal antibody directed against the HER-2/neu (c-erbB-2) oncoprotein. This protein is encoded by the HER-2/neu gene. It has been characterized as a transmembrane growth factor receptor belonging to the epidermal growth factor receptor family and is overexpressed in approximately 25–30% of all human breast cancers [1, 2]. Preclinical and clinical studies have shown the ability of trastuzumab to inhibit tumor growth in HER2-overexpressing metastatic breast cancer (MBC) [3].

Single-agent trastuzumab yielded a response rate of 24% in first-line treatment of MBC [4, 5], while a response rate of 15% was observed in second-line situations [6]. When trastuzumab was added to first-line chemotherapy, the response rate increased from 25% in patients treated with single-agent paclitaxel to 57.3% in patients receiving a combination of paclitaxel and trastuzumab [2, 7, 8]. The combination of trastuzumab and docetaxel yielded response rates of 61% compared to 34% (p = 0.002) in patients having received docetaxel alone [9]. Additionally, it was shown that first-line use of trastuzumab together with chemotherapy significantly increases median survival from 20.0 months to 25.4 months (p = 0.045) after a median follow-up of 25 months [2]. It was concluded that trastuzumab acts synergistically when added to chemotherapy.

Despite these improvements in the treatment of HER2 overexpressing MBC, views still differ on how to deal with patients who progressed during treatment with trastuzumab. Although high response rates to second- or third-line trastuzumab-based regimens have been reported, it still remains unclear whether trastuzumab should be continued beyond disease progression. Two studies were able to demonstrate a beneficial effect of the continuation of trastuzumab beyond progression [10, 11], which is supported by this retrospective evaluation.

Patients and Methods

Patient Recruitment

This retrospective analysis evaluates 136 patients with HER2 3+ MBC, treated between March 2000 and May 2004. Patients were recruited from 3 outpatient oncological wards, including the University Hospital of Munich, Germany. Patient recruitment was based on the electronic review of the data banks of each participating center. Criteria for review were 'HER2 overexpression', 'DAKO 3+' and 'metastatic breast cancer'.

All patients commencing on trastuzumab were shown to have HER2 overexpressing MBC on the basis of an immunohistochemical staining score (DAKO 3+, DAKO Hercep Test™, Dako, Copenhagen, Denmark). For the majority of patients (n = 124), determination of the HER2 status by immunohistochemistry (IHC) was carried out centrally (University Hospital of Munich).

Trastuzumab-Based Treatment

Trastuzumab was given according to the standard regimen at a loading dose of 4 mg/kg, followed by weekly doses of 2 mg/kg, either as a single agent or in combination with chemotherapy. In addition to trastuzumab, most patients received chemotherapy at the discretion of the treating physician.

Patient Assessment

All data were analyzed retrospectively. The clinical course, including sites of disease and best response to therapy in those sites, was reviewed on an intent-to-treat basis.

In all patients, tumors were measured by imaging procedures, such as CT or MRI. Patient response was assessed by the following standard WHO criteria: complete response (CR) was defined as the disappearance of all

Table 1. Baseline characteristics of breast cancer patients (n = 136) at presentation

Baseline characteristics	All patients, n (%)	Patients in subgroup 1[b], n (%)	Patients in subgroup 2[c], n (%)
Patients	136 (100)	113 (100)	23 (100)
HER2 status (DAKO 3+)	136 (100)	113 (100)	23 (100)
Median age (range; years)	58 (35–87)	59 (36–87)	57 (35–72)
Size of primary lesion			
T1	36 (26.5)	30 (26.5)	6 (26.1)
T2	64 (47.1)	54 (47.8)	10 (43.5)
T3	17 (12.5)	12 (10.6)	5 (21.7)
T4	19 (13.9)	17 (15.1)	2 (8.7)
Nodal status			
N0	41 (30.1)	34 (30.1)	7 (30.4)
N+	95 (69.9)	79 (69.9)	16 (69.6)
Metastases			
M0	107 (78.7)	89 (78.8)	18 (78.3)
M+	29 (21.3)	24 (21.2)	5 (21.7)
Hormone receptor status			
ER or PR positive	96 (70.6)	79 (69.9)	17 (73.9)
ER and PR negative	40 (29.4)	34 (30.1)	6 (26.1)
Grading of primary lesion			
G1	1 (0.7)	1 (0.9	0
G2	52 (38.2)	41 (36.3)	11 (47.8)
G3	83 (61.0)	71 (62.8)	12 (52.2)
Surgery	107 (78.7)		
Radiotherapy	59 (43.4)		
Adjuvant treatment			
Anthracyclines	56 (41.2)		
Taxanes	27 (19.9)		
High-dose therapy + PBSCT	5 (3.7)		
Hormonal	58 (42.6)		
Site of metastasis[a]			
Liver	74 (54.4)		
Lung	52 (38.2)		
Bone	73 (53.7)		
Soft tissue (lymph nodes)	55 (40.4)		
Number of metastatic sites			
1	37 (27.2)	35 (31.0)	2 (8.7)
2	51 (37.5)	40 (35.4)	11 (47.8)
≥ 3	48 (35.3)	38 (33.6)	10 (43.5)

[a] Patients were mentioned twice due to 2 or more metastatic sites (sum > 100%).
[b] 1 trastuzumab-based therapy.
[c] > 1 trastuzumab-based therapy.

Table 2. MBC treatment: description of types of treatment, duration and response (total number of patients: 136)

Type of treatment	Patients, n (%)	Median duration of treatment, weeks	Response, %
First-line therapy			
Hormonal	29 (21.3)		
Chemotherapy (including trastuzumab-based)	107 (78.7)		
Anthracyclines	36 (26.5)[a]		
Taxanes	18 (13.2)[a]		
Anthracyclines + taxanes	13 (9.6)[a]		
Other regimens	53 (49.5%)[a]		
Trastuzumab-based therapy – first-line		29.5 (1–358)	37.9 (22.1–43.7[b])
Trastuzumab plus taxane	25 (37.9)[a]		
Trastuzumab plus vinorelbine	28 (42.4)[a]		
Single-agent trastuzumab	13 (19.7)[a]		
Trastuzumab-based therapy – second-line		25 (1–186 weeks)	35.7 (20.9–41.6[b])
Taxane	26 (37.1)[a]		
Vinorelbine	15 (21.4)[a]		
Other	3 (4.3)[a]		
Single-agent trastuzumab	3 (4.3)[a]		
Trastuzumab continuation beyond progression	23 (16.9)	55 (5–156)	first regimen: 56.6 (30.1–74.2[b]) second regimen: 39.1 (17.6–60.7[b])

[a] Percentages calculated for subgroups.
[b] 95% CI.

known disease determined by 2 observations no less than 4 weeks apart, and partial response (PR) was defined as an at least 50%-decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions determined by 2 observations no less than 4 weeks apart. Stable disease (SD), lasting for at least 6 weeks from the start of the study (i.e. first drug administration), was defined as a < 50% decrease and a < 25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease (PD) was a > 25% increase in the size of at least 1 bidimensionally or unidimensionally measurable lesion or the appearance of a new lesion. The occurrence of pleural effusion was considered to be a sign of progression if it could be substantiated by positive cytology.
Continuation of trastuzumab single-agent or trastuzumab-based regimen despite tumor progression to upfront treatment with trastuzumab +/– chemotherapy was defined as treatment beyond progression.

Statistical Analysis
Overall survival was measured from the initial diagnosis of systemic metastatic disease until death from any cause (intent-to-treat). Probability of survival was estimated by Kaplan-Meier analysis [12]. Confidence intervals for response rates were calculated using methods for exact binominal confidence intervals [13]. The log rank test was used to describe different groups of patients.

Results

Patient Characteristics (n = 136)
HER2 expression determined by IHC was 3+ (DAKO Hercep Test) in all patients. The median age was 58 years (range: 35–87 years). 83 patients had received adjuvant chemotherapy (61%) including anthracyclines in 56 patients (67.5%), taxanes in 27 patients (32.5%), high-dose chemotherapy with autologous stem cell support in 5 patients (6%) and hormonal therapy in 58 patients (69.9%). The majority of patients suffered from visceral metastases. Patient characteristics at presentation of the entire study population are presented in table 1.

Response to Treatment
Upfront treatment including trastuzumab was given to 66 patients (48.5%). Of those, 13 patients (19.7%) received single-agent trastuzumab, 25 patients (37.9%) received trastuzumab plus taxanes, and 28 patients (42.4%) received trastuzumab plus vinorelbine. The median duration of trastuzumab-based treatment was 29.5 weeks (range: 1–358 weeks). The overall response rate was 37.9% (95% confidence interval, CI: 22.1–43.7%).
Out of 136 patients 23 received trastuzumab-based treatment beyond disease progression after a trastuzumab-based regimen given as first-line MBC treatment. All of them had received a combination therapy with taxanes or vinorelbine either as first- or second-line regimen (n = 23; 100%). Further trastuzumab-based combinations included gemcitabine (n = 3; 13%), cisplatin (n = 2; 8.7%) and capecitabine (n = 2; 8.7%). The overall response rate to the first and second trastuzumab-based regimen was 56.6% (95% CI: 30.1–74.2%) and 39.1% (95% CI: 17.6–60.7%), respectively.
47 patients received trastuzumab-based treatment as second-line therapy (34.6%). In this group, single-agent trastuzumab

was given to 3 patients (4.3%), while 26 received trastuzumab plus taxanes (37.1%), and 15 patients received trastuzumab plus vinorelbine (21.4%). 3 patients received other trastuzumab-based regimens (4.3%). The median duration of trastuzumab-based treatment was 25 weeks (range: 1–186 weeks). The overall response rate was 35.7% (95% CI: 20.9–41.6%). There were no cases of treatment-related grade 3 or 4 cardiotoxicity. An overview of the response to trastuzumab-based therapy is given in table 2.

Probability of Survival

The median overall survival of the study population calculated from first diagnosis of metastasis was 42.7 months (range 1–112 months). There was no difference in survival of patients who had received upfront trastuzumab and those who had not (p = 0.47 log rank). Moreover, the influence on survival of drugs combined with first-line trastuzumab seems to be limited (upfront vinorelbine or taxane; p = 0.58 log rank). Significant improved survival was only shown in patients who received trastuzumab-based treatment beyond disease progression compared to those who received only 1 trastuzumab-based regimen (1 vs. ≥ 2 trastuzumab-based regimens: 38.5 vs. 62.4 months; p = 0.01 log rank; fig. 1).

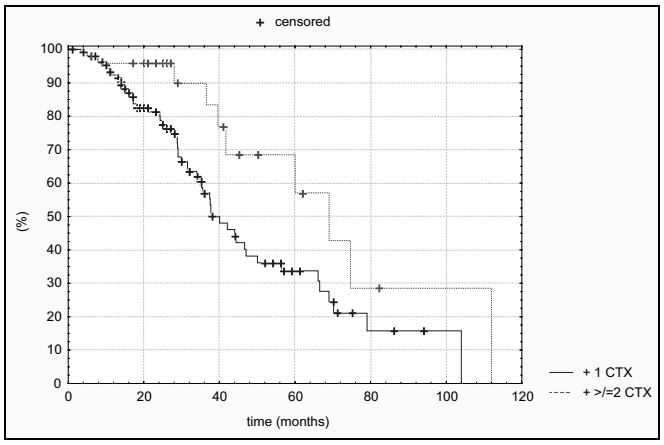

Fig. 1. Survival of patients who had received 1 vs. ≥ 2 trastuzumab-based chemotherapy for HER2 overexpressing MBC (n = 23; median 38.5 vs. 62.4 months; p = 0.01 log rank).

Discussion

The aim of this retrospective analysis was to characterize the clinical course of patients who received trastuzumab-based therapies for HER2 overexpressing MBC. A specific focus was put on the question of how to deal with patients who progressed during trastuzumab-based treatment for HER2 overexpressing MBC.

Upfront treatment of HER2 overexpressing MBC with trastuzumab and chemotherapy significantly increased median survival from 20.0 months to 25.4 months (p = 0.045) after a median follow-up of 25 months [2]. Despite these beneficial improvements in the treatment of HER2-overxpressing patients, views still differ on how to deal with patients who progressed during trastuzumab-based treatment. Although treatment beyond progression would represent a new paradigm in oncological therapy, 2 published studies support this approach [10, 11].

Gelmon et al. reported 105 patients who received trastuzumab alone or in different combinations beyond disease progression. The overall survival in their trial was 29 months. Interestingly, responses to trastuzumab alone or in combination with taxanes or vinorelbine given as first- or second-line therapy were studied independently [10]. The response to first-line trastuzumab-based therapy was 39%, while the response rate to second-line trastuzumab as single-agent treatment or in combination with paclitaxel or vinorelbine was 36% and 38%, respectively. [10]. Patients who had not responded to the first treatment, subsequently responded to a second trastuzumab-based regimen. [10]. These findings are supported by another study by Tripathy et al. [11]. Patients treated in the 'Extension Study' received trastuzumab either as a single-agent or in various combinations after prior participation in a study, where patients had been randomly assigned to chemotherapy (group 1) or chemotherapy plus trastuzumab (group 2). Clinical benefit rates of 22% (group 1) and 32% (group 2) to single-agent trastuzumab and various combinations were reported. The median duration of response exceeded 6 months. There was no significant difference regarding the duration of trastuzumab-based treatment between both groups (group 1: 30 weeks vs. group 2: 26 weeks). Interestingly, patients who had received first-line trastuzumab in the prior study, showed improved median survival compared to those who crossed over to receive trastuzumab in the 'Extension Study' (25.1 vs. 20.3 months; p = 0.046) [2, 11]. In contrast, the data of our analyses did not support the findings of Tripathy et al., since the influence of first- or second-line trastuzumab on survival seems to be limited. These unexpected results may be explained by the retrospectivity and the imbalanced patient numbers of each subgroup of the study.

There was no difference regarding the response rates of first-line vs. second-line trastuzumab-based treatment (37.9% vs. 35.7%). But as indicated by the above-mentioned studies, patients who received a trastuzumab-based regimen beyond disease progression survived significantly longer than patients who received only 1 trastuzumab-based regimen for metastatic disease (38.5 vs. 62.4 months; p = 0.01 log rank). This is particularly noteworthy, as obviously there were no differences between those subgroups of patients with respect to the baseline characteristics.

With the increasing use of trastuzumab for HER2 overexpressing breast cancer, more patients will present with progressive disease during treatment with trastuzumab-based regimens. Clearly, the retrospective character of this analysis rep-

resents a limitation to any evaluation, and most likely there is a bias analyzing and comparing the outcomes of different groups. Although data from a retrospective analysis should be interpreted with caution, the data of our analysis and the data of 2 previously published trials by Tripathy et al. and Gelmon et al. indicated a beneficial effect of trastuzumab continuation beyond disease progression. Definitive data may only be derived from presently ongoing prospective trials, as for example the Herceptin-TBP trial of the German Breast Group (GBG, Intergroup Study BIG-3–05).

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